Initial Risk-Based Prioritization of High Production Volume (HPV) Chemicals

1,3-Diphenylguanidine (CASRN 102-06-7)
(CA Index Name: Guanidine, N,N'-diphenyl)

Prioritization Decision: Medium Priority.

- **In order to further evaluate the medium potential risk to pregnant women from the developmental toxicity associated with this chemical, and the medium potential risk to aquatic organisms, EPA has identified next steps involving efforts to develop a better understanding of exposures to this chemical. Examples of information that would assist EPA in its analysis include, but are not limited to:**
  - **Information concerning worker exposures to this chemical, including engineering and process controls, industrial hygiene practices, and stewardship activities that would affect the potential for pregnant workers to be exposed; and**
  - **Information concerning potential exposures of pregnant women to this chemical in consumer products, including data on its presence and concentration in products and formulations, and on consumer use activity patterns, considering the frequency and duration of exposures.**
  - **Information concerning releases of this chemical to the environment from manufacturing, processing, use, and disposal.**
  - **Other information pertinent to potential environmental exposures to this chemical.**
- **As an initial step in developing this understanding, companies that manufacture, process, or use this chemical are encouraged to provide available information on a voluntary and non-confidential basis.**

Screening-level prioritizations are interim evaluations that do not constitute either final Agency determinations as to risk or final determinations as to whether sufficient data are available to characterize risk. They are based predominantly on screening-level hazard, exposure, and risk characterizations prepared by EPA using data submitted to the Agency under the HPV Challenge Program[1] and the 2006 Inventory Update Reporting (IUR)[2], and data publicly available through other selected sources. These screening-level characterizations do not constitute full risk assessments. They are intended only to support initial decisions to determine the relative priority for further assessment or risk management activities concerning HPV chemicals, and to identify data needs for individual chemicals or chemical categories. The methodology used in preparing these characterizations and prioritization decisions is available on the EPA website.[3]

[1] US EPA, HPV Challenge Program information: http://www.epa.gov/hpv/.
[2] US EPA, IUR information: http://www.epa.gov/oppt/iur/index.htm.
[3] US EPA, Methodology for Risk-Based Prioritization Under ChAMP: http://www.epa.gov/champ/pubs/rbp/method.pdf.

Screening-Level Characterization Summary

Risk Characterization

Potential Risk to Aquatic Organisms from Environmental Releases: *MEDIUM.*
Although there is a high potential for exposure to this chemical, the moderate acute hazard for aquatic organisms suggests a medium potential risk to aquatic organisms from environmental releases.

Potential Risk to the General Population, Workers, and Consumers: *MEDIUM.* The potential for exposure is high to these populations. The animal data suggest a low potential hazard for most adults, but a moderate hazard for pregnant women. Thus, there is a potential medium risk to pregnant women exposed to this chemical.

Potential Risk to Children: *LOW.* Although the potential for exposure is high, the low human health hazard suggests a low potential risk to children exposed to this chemical.

Production Volume, Use, and Release Information

This chemical has an aggregated production and/or import volume in the U.S. of 1 million to 10 million pounds.

Non-confidential IUR information indicates that the industrial processing and uses of the chemical include process regulators in vulcanization or polymerization processes. Non-confidential information in the IUR indicates that the commercial and consumer products containing the chemical include rubber and plastic products. Information from the HSDB indicates that this chemical is primarily used as a vulcanization accelerator for rubbers.

No information is available on releases of this chemical to the environment.

Hazard Characterization Summary

This chemical is a solid with moderate water solubility and low vapor pressure. It is a weak base with a pK_a of 10.12 and exists primarily as its conjugate acid under environmental conditions. Volatilization is considered low since ionic species are expected to have low vapor pressure. The rate of hydrolysis is expected to be negligible under environmental conditions. The rate of atmospheric photodegradation is considered moderate. This chemical is expected to have moderate persistence (P2) and low potential for bioaccumulation (B1).

The evaluation of available toxicity data for aquatic organisms indicates that the potential hazard is moderate for fish, aquatic invertebrates and aquatic plants.

The acute oral toxicity of this chemical in rats is moderate and the acute dermal toxicity in rabbits is low. It is not irritating to rabbit skin, but is slightly irritating to rabbit eyes. In oral repeated-dose toxicity studies, there was low systemic toxicity in rats and mice. Prenatal developmental toxicity studies showed moderate maternal toxicity and moderate developmental

toxicity in rats, and no maternal or developmental toxicity in mice. A sperm morphology and male fertility study in mice did not show any signs of developmental or reproductive toxicity. Sperm morphology and vaginal cytology examinations showed no toxicity in male and female rats and mice. Data from the repeated dose toxicity study in rats did not show any effects to reproductive organs. This chemical did not induce gene mutations *in vitro* and did not induce chromosomal aberrations *in vivo*. It did not cause skin sensitization in guinea pigs, although positive reactions occurred in humans.

No data gaps were identified under the HPV Challenge Program.

Exposure Characterization Summary

EPA identifies a high potential that the general population and environment might be exposed to this chemical based on the industrial processing and use information, the production volume, the potential for environmental releases, and the moderate persistence.

EPA identifies a high relative ranking for potential worker exposure based on potential for exposure to particulates and the number of potentially exposed workers.

EPA identifies a high potential that consumers and children might be exposed to this chemical based on IUR data and other public data sources, including the HPV submission and the Source Ranking Database, that indicate its presence in consumer products. IUR data indicate that children's use information is Not Readily Obtainable.

Additional Considerations for Prioritization Decision

Regulatory and Related Information Summary

- This chemical is on the TSCA Inventory, and is not otherwise regulated under TSCA.
- This chemical was identified as a high priority for health by Canada in its review of the Canadian Domestic Substance List, and will be addressed in Batch 12. The current schedule contemplates that Canada would release a profile on this substance and request additional information in November 2009, with the risk assessment to be completed approximately one year later.

Assumptions and Uncertainties

- EPA has no information on releases of this chemical, and has made assumptions about potential exposures based on generic use scenarios associated with reported uses. The lack of environmental release data for a chemical is a source of uncertainty in the potential that the general population and the environment might be exposed to that chemical.
- EPA has no information on the use of this chemical in products specifically intended to be used by children. Children's use of commercial/consumer products were reported in the IUR as Not Readily Obtainable. There is uncertainty surrounding the potential that children might be exposed to a chemical with consumer uses that are not specifically intended for children. EPA generally assumes a medium to high potential that children might be exposed to a

chemical with consumer uses that are not specifically intended for children. There is uncertainty surrounding the potential that consumers might be exposed to a chemical identified in IUR submissions as having commercial/consumer uses. EPA generally assumes a high potential that consumers might be exposed to a chemical with commercial/consumer uses.

Appendix A: Screening-Level Hazard Characterization

SPONSORED CHEMICAL

1,3-Diphenylguanidine (CASRN 102-06-7)
(CA Index Name: Guanidine, N,N'-diphenyl)

Introduction

The sponsor, American Chemistry Council (ACC) Rubber and Plastics Additives (RAPA) Panel, submitted a Test Plan and Robust Summaries to EPA for 1,3-diphenylguanidine on December 9, 2003. EPA posted the submission on the ChemRTK HPV Challenge website on January 14, 2004 (http://www.epa.gov/chemrtk/pubs/summaries/13dphnlg/c14886tc.htm). EPA comments on the original submission were posted to the website on May 13, 2004. Public comments were also received and posted to the website.

1. Physical-Chemical Properties and Environmental Fate

The physical-chemical properties of 1,3-diphenylguanidine are summarized in Table 1a, while the environmental fate properties are given in Table 1b. Its structure is provided in Table 2 at the end of Appendix A.

Physical-Chemical Properties Characterization

1,3-Diphenylguanidine is a solid with moderate water solubility and low vapor pressure.

Table 1a. Physical-Chemical Properties of 1,3-Diphenylguanidine[1]

Property	Value
CASRN	102-06-7
Molecular Weight	211.27
Physical State	Solid
Melting Point	147–150°C (measured)
Boiling Point	>200°C (measured)
Vapor Pressure	1.3×10^{-8} mm Hg at 20°C (extrapolated)
Water Solubility	475 mg/L at 25°C and pH 7 (measured)
Dissociation Constant (pK_a)	10.12
Henry's Law Constant	1.8×10^{-11} atm-m^3/mole (estimated)
Log K_{ow}	1.54–1.76 (measured)

[1]SIDS Initial Assessment Report for SIAM 14. 2002. Paris, France March 26-28. http://cs3-hq.oecd.org/scripts/hpv/. Full report available at: http://www.oecd.org/dataoecd/37/10/38274525.zip.

Environmental Fate Characterization

1,3-Diphenylguanidine is expected to have moderate mobility in soil. 1,3-Diphenylguanidine is not ready biodegradable. It did not degrade in two ready biodegradation tests (OECD 301D closed bottle test and OECD 301C modified MITI test); however, it was 75% biodegraded using an adapted sludge and therefore was classified as inherently biodegradable. 1,3-Diphenyl-

guanidine is a weak base with a pK_a of 10.12 and exists primarily as its conjugate acid (the guanidinium cation) under environmental conditions. Volatilization is considered since ionic species are expected to have low vapor pressure. The rate of hydrolysis is expected to be negligible under environmental conditions. The rate of atmospheric photooxidation is considered moderate. The persistence of 1,3-diphenylguanidine is considered moderate (P2) and the bioaccumulation potential is ranked low (B1) based on BCF values less than 20, measured in carp.

Table 1b. Environmental Fate Characteristics of 1,3-Diphenylguanidine[1]	
Property	**Value**
Photodegradation Half-life	2.3 hours (estimated)[2]
Hydrolysis Half-life	7 days at pH 10.5 and 80°C; Stable under environmental conditions
Biodegradation	0% in 28 days (not readily biodegradable); 0% in 20 days (not readily biodegradable); 75% in 28 days (inherently biodegradable); 55–71% in 28 days (inherently biodegradable)
Bioconcentration	BCF = <20 (measured in carp)
Log K_{oc}	3 (estimated)[2]
Fugacity (Level III Model)	Air = <1% Water = 35.5% Soil = 64.4% Sediment = <1%
Persistence[3]	P2 (moderate)
Bioaccumulation[3]	B1 (low)

[1]SIDS Initial Assessment Report for SIAM 14. 2002. Paris, France March 26-28. http://cs3-hq.oecd.org/scripts/hpv/. Full report available at: http://www.oecd.org/dataoecd/37/10/38274525.zip.
[2]U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.
[3]Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: 1,3-Diphenylguanidine is a solid with moderate water solubility and low vapor pressure. 1,3-Diphenylguanidine is a weak base with a pK_a of 10.12 and exists primarily as its conjugate acid (the corresponding guanidinium cation) under environmental conditions. Volatilization is considered low since ionic species are expected to have low vapor pressure. The rate of hydrolysis is expected to be negligible under environmental conditions. The rate of atmospheric photodegradation is considered moderate. 1,3-Diphenylguanidine is expected to have moderate persistence (P2) and low potential for bioaccumulation (B1).

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

(1) Fathead minnows (*Pimephales promelas*) were exposed to 1,3-diphenylguanidine at nominal concentrations of 0, 1.0, 1.8, 3.2, 5.6 or 10 mg/L under static conditions for 96 hours. Measured concentrations were not reported. Acetone was used as a solvent (66 mg/L), although not as a solvent control. Mortality (10%) was observed at 5.6 mg/L after 24 and 100% mortality after 96 hours and at 10 mg/L after 100% mortality was observed at 48 hours. Sublethal effects, noted as loss of equilibrium, were observed from at 3.2 mg/L and above.
96-h LC_{50} = 4.2 mg/L

(2) Rainbow trout (*Oncorhynchus mykiss*) were exposed to 1,3-diphenylguanidine at nominal concentrations of 0, 3.2, 5.6, 10, 18 or 32 mg/L under static conditions for 96 hours. Measured concentrations were not reported. Acetone was used as a solvent (213 mg/L), although not as a solvent control. Mortality (20%) was observed at 10 mg/L after 24 and 40% mortality after 96 hours, 30 % mortality was observed at 18 mg/L after 24 and 100% after 96 hours, and 100% mortality was observed at 32 mg/L after 24 hours. Sublethal effects, noted as loss of equilibrium, were observed at 10 and 18 mg/L.
96-h LC_{50} = 11 mg/L

(3) Bluegill sunfish (*Lepomis macrochirus*) were exposed to 1,3-diphenylguanidine at nominal concentrations of 0, 7.5, 14, 24, 42 or 75 mg/L under static conditions for 96 hours. Measured concentrations were not reported. Acetone was used as a solvent (1000 mg/L), although not as a solvent control. Mortality (20%) was observed at 7.5 mg/L after 96 hours, 90- 100% mortality was observed at 14 mg/L after 72 – 96 hours and 100% mortality was reported at 24 – 75 mg/L after 24 hours. Sublethal effects, noted as loss of equilibrium, were observed from at 7.5 and 14 mg/L.
96-h LC_{50} = 9.6 mg/L

Acute Toxicity to Aquatic Invertebrates

(1) *Daphnia magna* were exposed to 1,3-diphenylguanidine at nominal concentrations of 0, 1.4, 2.8, 5.5, 11, 22, 44, 88 or 177 mg/L under static conditions for 24 hours. Measured concentrations were not reported. Immobility ranged from 0% at ≤ 22 mg/L to 100% at 177 mg/L.
24-h EC_{50} = 73.6 mg/L

(2) *Daphnia magna* were exposed to 1,3-diphenylguanidine at nominal concentrations of 0, 3.2, 5.6, 10, 18 or 32 mg/L under static conditions for 48 hours. Measured concentrations were not reported. Acetone was used as a solvent control (1600 mg/L). Immobility was seen at 18 and 32 mg/L.
48-h EC_{50} = 17 mg/L

Toxicity to Aquatic Plants

(1) Green algae (*Pseudokirchneriella subcapitata*) were exposed to 1,3-diphenylguanidine at nominal concentrations of 0.01, 0.032, 0.1, 0.32, 1.0, 3.2, 10.0, 32.0 or 100.0 mg/L for 72 hours. Measured concentrations were not reported.
72-h EC_{50} (biomass) = 2.6 mg/L
72-h EC_{50} (growth) = 7.5 mg/L

(2) Green algae (*Pseudokirchneriella subcapitata*) were exposed to 1,3-diphenylguanidine at nominal concentrations of 0, 0.3, 0.6, 1.0, 3.2 or 5.6 mg/L for 72 hours. Solvent (dimethyl formamide) exceeded the acceptable concentration; however, solvent control results were similar to control.
72-h EC_{50} (growth) = 2.0 mg/L
96-h EC_{50} (Biomass) = 1.4-1.7 mg/L

Chronic Toxicity to Aquatic Invertebrates

Daphnia magna were exposed to 1,3-diphenylguanidine at nominal concentrations ranging from 0.6 to 60 mg/L under semi-static conditions for 21 days. Measured concentrations were not reported. There was no adult mortality up to 1.9 mg/L, although 100% mortality occurred within 5 – 7 days at 6.0 – 60 mg/L. At 1.9 mg/L, a 19.8% decreased reproduction rate was observed.
21-d NOEC = 0.6 mg/L (reproduction rate)
21-d LOEC = 1.9 mg/L (reproduction rate)
21-d EC_{50} = 1.9 – 6.0 mg/L (reproduction rate)

Conclusion: The evaluation of available toxicity data for aquatic organisms indicates that the potential hazard of 1,3-diphenylguanidine to fish, aquatic invertebrates and aquatic plants is moderate.

3. Human Health Effects

Acute Oral Toxicity

(1) Male and female Sprague-Dawley rats (total number reported as 30) were administered doses of 1,3-diphenylguanidine in corn oil ranging from 290-420 mg/kg-bw.
LD_{50} = 350 mg/kg-bw

(2) Male Sprague-Dawley rats (10/dose) were administered doses of 1,3-diphenylguanidine in corn oil at doses ranging from 100-1000 mg/kg-bw and observed for 14 days after exposure. Mortality occurred at doses of 170 mg/kg-bw and higher.
LD_{50} (male) = 460 mg/kg-bw

(3) Female Sprague-Dawley rats (10/dose) were administered doses of 1,3-diphenylguanidine in corn oil at doses ranging from 100-1000 mg/kg-bw and observed for 14 days. Mortality occurred at doses of 170 mg/kg-bw and higher.
LD_{50} (female) = 384 mg/kg-bw

Acute Dermal Toxicity

New Zealand White rabbits (5/sex/dose) were dermally administered 2000 mg/kg-bw of 1,3-diphenylguanidine and observed for 14 days. No mortality occurred during the study.
LD_{50} > 2000 mg/kg-bw

Repeated-Dose Toxicity

(1) Sprague-Dawley rats (15/sex/dose) were administered 1,3-diphenylguanidine via the diet at doses of 0, 50, 150 or 500 ppm for 13 weeks. Approximate daily doses reported in the robust summary were 0, 4, 11 or 37 mg/kg-bw/day. In both sexes, reductions on body weight were observed at 37 mg/kg-bw/day only; the other two dose groups were similar to controls. Body weight in the high-dose males was approximately 15% lower than controls ($p < 0.001$) for the majority of the exposure period; exceptions were weeks 9, 10 and 13 (2, 19 and 21%, respectively). Body weight reduction in the high-dose females was 9% at week 1 and 16 – 18% at weeks 9 – 13 ($p < 0.001$). Food consumption was also reduced in both sexes at 37 mg/kg-bw/day (statistical significance not provided); this effect was most pronounced during the first few weeks of the study, suggesting, according to the robust summary, poor palatability of test substance as a possible cause. Reductions in absolute organ weights and increased relative organ weights in both sexes at 37 mg/kg-bw/day were reported, apparently reflecting the decreases in body weight; relative organ weights that were increased included kidneys, adrenals, pituitary and testes in males, and lungs, spleen and uterus in females. The gross and histopathological examinations showed no lesions in any tissues that were dose-related or attributable to exposure. No mortality or abnormal clinical signs that could be attributed to the test substance were reported.
NOAEL ~ 37 mg/kg-bw/day (based on no adverse signs of toxicity at the highest dose tested)

(2) In a NTP study in F344 rats, 10/sex/dose were administered 1,3-diphenylguanidine via the diet at doses of 0, 250, 500, 750, 1500 or 3000 ppm for 13 weeks (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.searchhome). Approximate daily doses in the males/females were 0/0, 17/17, 32/32, 50/49, 100/95 or 181/184 mg/kg-bw/day, respectively. Clinical signs of toxicity (thin appearance, staggering, salivation, hypoactivity, convulsions and seizures, among others) occurred in some (number not provided) male and female rats at 100/95 mg/kg-bw/day or higher within two weeks of exposure. Mortality was increased (6/10 males; 100% in females) at the highest dose. Decreased food consumption (due to poor palatability) was observed at the two highest dose groups; mean body weights in males and females were lower than controls at those same dose groups. Hematological changes consisted of a mild polycythemia (increased erythrocyte counts, hematocrit values and hemoglobin concentrations) and slightly reduced reticulocyte counts in females at ≥ 95 mg/kg-bw/day and both sexes at 181/184 mg/kg-bw/day only at day 5. Serum total protein, creatinine, cholesterol and triglyceride concentrations were reduced at ≥ 100/95 mg/kg-bw/day and were consistent with lack of food. Gross necropsy observations included thinness of the carcass, and histopathological changes in the bone marrow, thymus, uterus, testes, prostate gland/seminal vesicle and salivary glands at ≥ 100/95 mg/kg-bw/day. The NTP report concluded the observed

body weight, hematological and blood chemistry changes, and gross and microscopic changes were not attributable to chemical exposure but instead indicative of reduced nutrient intake (food and water), consistent with similar changes observed in studies of feed restricted rats.
LOAEL ~ 100/95 mg/kg-bw/day (based on clinical signs of toxicity)
NOAEL ~ 50/49 mg/kg-bw/day

(3) In a NTP study in B6C3F1 mice, 10/sex/dose were administered 1,3-diphenylguanidine via the diet at doses of 0, 250, 500, 750, 1500 or 3000 ppm for 13 weeks (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.searchhome). Approximate daily doses in the males/females were 38/46, 75/93, 114/141, 231/285 or 457/577 mg/kg-bw/day. Reduced body weight compared to controls was observed in both sexes at the three highest doses (statistical significance not provided). Mean body weights of male mice in the 457 mg/kg-bw/day dose group were generally between 80% to 90% of control; mean feed consumption for the study was 93% of control. Clinical signs included thin appearance in females at ≥ 141 mg/kg-bw/day and males at 457 mg/kg-bw/day; alopecia, abnormal posture, ptosis and bristly hair were also observed in both sexes at the higher doses (doses not specified in robust summary). Reductions in absolute organ weights and increases in relative organ weights were observed for several unspecified organs at ≥ 231/285 mg/kg-bw/day (statistical significance not reported); the NTP report concludes that these effects were not indicative of a specific toxic response, but appeared to be the result of the lower body weights (due to reduced food intake/poor palatability). No treatment-related gross or histopathologic lesions were observed for either sex. The NTP report concluded the body weight and organ weight changes observed in mice were not attributable to chemical exposure but instead indicative of reduced nutrient intake (food and water), consistent with similar changes observed in studies of feed restricted rats.
LOAEL ~ 141 mg/kg-bw/day for females; 457 mg/kg-bw/day for males (based on clinical signs of toxicity)
NOAEL ~ 93 mg/kg-bw/day for females; 231 mg/kg-bw/day for males

Reproductive Toxicity

(1) Male CD-1 mice (25/dose) were administered 1,3-diphenylguanidine via gavage at 0, 0.06, 0.25, 1, 4 or 16 mg/kg-bw/day for 8 weeks prior to mating with untreated females in order to evaluate the effect of oral administration of 1,3-diphenylguanidine on sperm morphology and male fertility in mice. Body weight and mortality were evaluated during the exposure period. Within 24 hours after the last exposure, 9 – 13 males were selected from each dose group and used for gross necropsy and organ weight evaluations (all doses) and testicular histology and sperm abnormality evaluations (0 and 16 mg/kg-bw/day). Remaining males in the 0, 4 and 16 mg/kg-bw/day were mated with untreated females within 14 days after the last exposure; evaluations included fertility, reproductive performance and litter endpoints. During the treatment period, an unspecified small number of animals from all doses, except the 0 and 0.06 mg/kg-bw/day, were found dead or moribund; the robust summary states the cause of these deaths were either due to dosing errors or were undetermined. No differences in weight gain, clinical observations, or organ weights were observed between the control group and any of the treated groups. Microscopic examination of the testes of mice in the control and 16 mg/kg-bw/day groups did not reveal any treatment-related abnormalities. There was a slight increase in sperm cells with folded tails in the 16 mg/kg-bw/day (5 versus 2% in controls), but the

toxicological significance was unclear because there were no effects on the frequency of total sperm abnormalities or testicular histology. Male or female fertility and reproductive performance were comparable at all doses examined and maternal necropsy findings and litter data did not indicate any chemical-related effects on embryonic/fetal development.
NOAEL (male reproductive toxicity) = 16 mg/kg-bw/day (based on no effects at highest dose tested)

(2) At the end of the NTP 13-week dietary study in F344 rats described previously, vaginal cytology and sperm motility evaluations were performed. Male endpoints included sperm count, morphology and motility; testis, epididymis and cauda epididymis weights; and histopathology of testis, epididymis and seminal vesicle. Female endpoints included estrous cycle length, relative frequency of estrous stages and histopathology of ovary and uterus. (The methods used were those outlined in the 1987 NTP Technical Protocol for Sperm Morphology and Vaginal Cytology Evaluation in Toxicity Testing for Rats and Mice). Effects in the male rats included reduced sperm motility at 100 mg/kg-bw/day and sporadically occurring histopathological changes in the testes (reduced numbers of spermatozoa in seminiferous and epididymal tubules) and accessory sex glands (secretory depletion of the prostate and seminal vesicles) at 181 mg/kg-bw/day. Effects in the female rats included increased estrous cycle length and uterine hypoplasia (overall reduction in size of uterus) at ≥ 49 mg/kg-bw/day. The histopathological and corresponding functional changes observed in both male and female rats were interpreted in the NTP report as being a reflection of physiological atrophy due to reduced nutrient intake (food and water due to poor palatability) and are consistent with similar changes observed in other studies of feed restricted rats.
NOAEL (male and female reproductive toxicity) = 181/184 mg/kg-bw/day (highest dose tested)

(3) At the end of the NTP 13-week dietary study in B6C3F1 mice described previously, vaginal cytology and sperm motility evaluations were performed. Male endpoints included sperm count, morphology and motility; testis, epididymis and cauda epididymis weights; and histopathology of testis, epididymis and seminal vesicle. Female endpoints included estrous cycle length, relative frequency of estrous stages and histopathology of ovary and uterus. (The methods used were those outlined in the 1987 NTP Technical Protocol for Sperm Morphology and Vaginal Cytology Evaluation in Toxicity Testing for Rats and Mice). Effects in the mice included increased number of spermatid heads and reduced sperm density and sperm motility in males at 457 mg/kg-bw/day and increased estrous cycle length in females at 577 mg/kg-bw/day. No gross or microscopic lesions were observed and no other effects were reported. For male reproductive toxicity, the NTP report concluded that the increase in the number of spermatid heads in the testis coupled with a lower number of sperm in the epididymus suggests that 1,3-diphenylguanidine does not impair sperm formation in the testis but may affect the release of sperm into the epididymus. The NTP report concluded that the mean body weights of male mice in the 457 mg/kg-bw/day dose group were generally between 80% to 90% of control; mean feed consumption for the study was 93% of control. Studies with a different strain of mice (Swiss CD-1) did not show testicular and epididymal sperm effects when food was restricted at these levels; only when food restriction reached 70% of control body weight. The NTP report concluded that although the data in the present study suggests potential male chemical–related reproductive toxicity, the response to feed restriction in male B6C3F1 mice may differ from that

of male CD-1 mice. For female reproductive toxicity, the report concluded the lengthening of the estrous cycle was a consequence of the low body weights and reduced feed consumption rather than a chemical-related effect.
NOAEL (male and female reproductive toxicity) = 457/577 mg/kg-bw/day (highest dose tested)

(4) In the 13-week dietary study in Sprague-Dawley rats described previously, evaluations of male and female reproductive organ weights and histology were performed on the testis, epididymis, seminal vesicle, and uterus. Increases in relative weights of testes (25%) and uterus (34%) were observed at 37 mg/kg-bw/day, but there were no corresponding histopathological changes in these or other tissues.

Developmental Toxicity

(1) Pregnant Sprague-Dawley rats (25/dose) were administered 1,3-diphenylguanidine via gavage at 0, 5, 25 or 50 mg/kg-bw/day in 0.5% aqueous Methocel on days 6 – 15 of gestation; dams were sacrificed on gestation day 20. The doses were selected based on the results of a preliminary range finding study. At 50 mg/kg-bw/day, maternal mean body weight gain was significantly ($p < 0.01$) decreased. Numerous clinical signs, including alopecia, tachypnea, decreased limbtone, prostration, lethargy and/or ataxia were observed in all animals; hypersensitivity to touch, salivation and piloerection occurred in a few animals. At 50 mg/kg-bw/day signs of developmental toxicity included a slight increase in mean post implantation loss, a significant decrease in mean fetal body weight, and an increased number of fetuses with skeletal variations (unossified sternebrae #5 and/or #6, reduced ossification of the 13th ribs, 25 presacral vertebrae and bent ribs); these results were not quantitatively reported in the robust summary and statistical significance was not noted.
LOAEL (maternal toxicity) = 50 mg/kg-bw/day (based on slight reduced body weight gain)
NOAEL (maternal toxicity) = 25 mg/kg-bw/day
LOAEL (developmental toxicity) = 50 mg/kg-bw/day (based on reduced fetal body weight and increased skeletal variations)
NOAEL (developmental toxicity) = 25 mg/kg-bw/day

(2) Pregnant ICR mice (20/dose) were administered 1,3-diphenylguanidine in 0.5% carboxymethyl cellulose solution via gavage at 0, 0.25, 1, 4 or 10 mg/kg-bw/day on days 0 – 18 of gestation (Yasuda and Tanimura, 1980). The animals were sacrificed on gestation day 18 for uterine and fetal examinations. No signs of maternal toxicity were reported. There was a difference in the number of pregnant females at the 10 mg/kg-bw/day dose group compared to the rest of the groups (7 compared to 19 or 20 in the control and other dose groups), but the study authors did not address this difference and therefore, it is not clear if that was the original number of dams in that group or if there was maternal mortality. The authors did state that selection of the highest dose in this study was based on the observation that all non-pregnant mice given a dose of 15 mg/kg-bw/day died within 6 days. Developmental endpoints included number of implantations, early and late fetal deaths, litter size and fetal body weight, sex ratio and abnormalities/variations (external, skeletal and soft tissue). The only effect observed was an 11% reduction in average number of implants per mouse at 10 mg/kg-bw/day ($p < 0.05$); however, given that there were no significant differences between treated and control groups in

embryonic survival, average litter size, sex ratio, or mean fetal body weights, the reduction in implantations in dams at the 10 mg/kg-bw/day dose group is equivocal. Data from the present study do not allow for a more definitive conclusion.
NOAEL (maternal/developmental toxicity) = 10 mg/kg-bw/day (based on no adverse effects reported at the highest dose tested)

Genetic Toxicity – Gene Mutation

In vitro
(1) *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to 1,3-diphenylguanidine at concentrations from 1 – 10,000 µg/plate in the presence and absence of metabolic activation. A weakly mutagenic or equivocal response in strains TA98 and TA100 with metabolic activation and an equivocal response in strain TA1537 with metabolic activation were observed. There was no indication of mutagenic activity in the absence of metabolic activation.
1,3-Diphenylguanidine was weakly/equivocal mutagenic in this assay.

(2) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to 1,3-diphenylguanidine at concentrations of 0.1 – 500 µg/plate in the presence and absence of metabolic activation. **1,3-Diphenylguanidine was not mutagenic in this assay.**

(3) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to 1,3-diphenylguanidine at concentrations of 2 – 500 µg/plate without metabolic activation and 20 – 5000 µg/plate with metabolic activation.
1,3-Diphenylguanidine was not mutagenic in this assay.

(4) *Escherichia coli* strain WP2uvrA was exposed to 1,3-diphenylguanidine at concentrations of 2 – 500 µg/plate without metabolic activation and 20 – 5000 µg/plate with metabolic activation.
1,3-Diphenylguanidine was not mutagenic in this assay.

(5) *Saccharomyces cerevisiae* strain D4 was examined for mutations following exposure to 1,3-diphenylguanidine at concentrations of 1 – 500 µg/plate in the presence and absence of metabolic activation. No additional information was provided in the robust summary.
1,3-Diphenylguanidine was not mutagenic in this assay.

(6) Mouse lymphoma L5178Y cells were examined for mutations following exposure to 1,3-diphenylguanidine at concentrations of 16.4 – 188 µg/mL without metabolic activation and 32.8 - 525 µg/mL with metabolic activation.
1,3-Diphenylguanidine did was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro
Chinese hamster ovary cells were exposed to 1,3-diphenylguanidine at concentrations of 125, 250, 500 or 750 µg/mL in the presence and absence of metabolic activation.
1,3-Diphenylguanidine did not induce cytogenetic effects in this assay.

In vivo

(1) Sprague-Dawley rats were administered 1,3-diphenylguanidine via gavage at doses of 0 (15/sex) or 300 mg/kg-bw (20/sex). The 300 mg/kg-bw dose level is a maximum tolerated dose (MTD) based on results of a range-finding study. Positive and vehicle control groups were included, and the positive control induced an appropriate response. 1,3-Diphenylguanidine was toxic to both sexes as evidenced by clinical signs (hypoactivity and nonresponsiveness) and some (five males and six female rats) deaths within 24 hours of dosing. Cytogenetic evaluation of bone marrow at 6, 24 and 48 hours after dosing showed no increases in the proportion of aberrant cells or aberrations/cell at any time point. Cytotoxicity, as indicated by a depression in mitotic index, was observed at the 6- and 24-hour time points.
1,3-Diphenylguanidine did not induce chromosomal aberrations in this assay.

(2) In the 13-week dietary study of 1,3-diphenylguanidine in B6C3F1 mice described previously, examinations for micronuclei in peripheral blood samples were performed. There was no increase in the frequency of micronucleated monochromatic erythrocytes in male mice. In females, the frequency of micronucleated erythrocytes was significantly increased at 141 mg/kg-bw/day (4.7-fold higher than controls, $p = 0.005$). The results in the female mice were judged to be equivocal because a marked increase in micronuclei only occurred at the middle dose and a statistically significant ($p > 0.025$) dose-related trend was not observed.
1,3-Diphenylguanidine was equivocal for induction of micronuclei in this assay.

Additional Information

Skin Irritation

Six rabbits (sex and strain not specified) were administered 0.5 g of 1,3-diphenylguanidine moistened with water under occlusive conditions for 24 hours. No erythema or edema was observed on intact or abraded skin up to 168 hours after treatment.
1,3-Diphenylguanidine was not irritating to rabbit skin.

Eye Irritation

(1) 1,3-Diphenylguanidine (20 mg) was instilled in the eyes of six rabbits (sex and strain not provided). Eyes were not rinsed following instillation. Severe erythema and very slight edema was observed at 1 and 24 hours. All irritation was gone by day 7.
1,3-Diphenylguanidine was slightly irritating to rabbit eyes.

(2) 1,3-Diphenylguanidine (100 mg) was instilled in the eyes of six rabbits (sex and strain not provided). Eyes were not rinsed following instillation. At 1 hour, moderate and very slight edema was observed. At 24 hours, severe erythema and slight to moderate edema was observed. The iris showed slow reaction to light at 1 hour and little to no reaction at 24 hours. At 21days, no irritation was seen.
1,3-Diphenylguanidine was irritating to rabbit eyes.

Skin Sensitization

(1) On day 1 of a guinea pig maximization test, 0.1 mL of 1.0% (w/w) 1,3-diphenylguanidine in paraffin oil was intradermally administered to 15 animals the presence of Freund's complete adjuvant. On day 8, 0.5 mL of 25% (w/w) 1,3-diphenylguanidine was cutaneously applied for 48 hours using an occlusive dressing. After 12 days without treatment, a challenge cutaneous application of 0.5 mL of 25% (w/w) 1,3-diphenylguanidine was applied for 24 hours using an occlusive dressing. No cutaneous reactions were observed at the challenge application sites when evaluated 24 and 48 hours after removal of the occlusive dressing.
1,3-Diphenylguanidine did not cause skin sensitization in guinea pigs.

(2) Patch testing of 49 volunteers with 0.2 g of 70% 1,3-diphenylguanidine in petrolatum produced no positive reactions following initial application. Nineteen of the 49 subjects displayed positive reactions during subsequent exposures during the induction phase, although only two subjects had positive reactions when rechallenged 2 weeks later at new exposure sites.
1,3-Diphenylguanidine caused skin sensitization in humans.

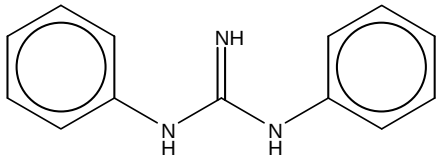
(3) Patch testing of 1670 and 317 patients with rubber components showed that 1,3-diphenylguanidine produced a positive response in 4.4% of those tested.
1,3-Diphenylguanidine caused skin sensitization in humans.

Conclusion: The acute oral toxicity of 1,3-diphenylguanidine to rats is moderate and the acute dermal toxicity to rabbits is low. Systemic toxicity of 1,3-Diphenylguanidine in the oral repeated-dose toxicity studies is low in rats and mice. Prenatal developmental toxicity studies showed moderate maternal toxicity and moderate developmental toxicity in rats and no maternal or developmental toxicity in mice. A sperm morphology and male fertility study in mice did not show any signs of developmental or reproductive toxicity. Sperm morphology and vaginal cytology examinations showed no toxicity in male and female rats and mice. Data from the 13-week repeated dose toxicity study in rats did not show any effects to reproductive organs. Available mutagenicity data suggest that 1,3-diphenylguanidine is not genotoxic. 1,3-Diphenylguanidine is not irritating to rabbit skin but is slightly irritating to rabbit eyes. 1,3-Diphenylguanidine did not cause skin sensitization in guinea pigs although positive reactions occurred in humans.

4. References

Yasuda, Y. and Tanimura, T. 1989. Effect of diphenylguanidine on development of mouse fetuses. Journal of Environmental Pathology and Toxicology, 4:451-456.

Table 2

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL 1,3-Diphenylguanidine (102-06-7)**
Structure	
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish **96-h LC_{50} (mg/L)**	4.2
Aquatic Invertebrates **48-h EC_{50} (mg/L)**	17
Aquatic Plants **72-h EC_{50} (mg/L)** **(growth)** **(biomass)**	 7.5 2.6
Aquatic Invertebrates **21-d NOEC (mg/L)** **21-d LOEC (mg/L)**	 0.6 1.9
Summary of Human Health Data	
Acute Oral Toxicity **LD_{50} (mg/kg-bw)**	350
Acute Dermal Toxicity **LD_{50} (mg/kg-bw)**	> 2000
Repeated-Dose Toxicity **NOAEL/LOAEL** **Oral (mg/kg-bw/day)**	(rat) NOAEL ~ 37 (mouse) NOAEL ~ 49 LOAEL ~ 95
Reproductive Toxicity **NOAEL/LOAEL** **Oral (mg/kg-bw/day)**	No treatment-related effects were seen following evaluation of reproductive organs and endpoints in 13-week oral repeated-dose toxicity studies in rats and mice. NOAEL = 16 (male, highest dose tested)

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL 1,3-Diphenylguanidine (102-06-7)**
Developmental Toxicity **NOAEL/LOAL** **Oral (mg/kg-bw/day)** **Maternal Toxicity** **Developmental Toxicity** **Maternal Toxicity** **Developmental Toxicity**	 (rat) LOAEL = 50 NOAEL = 25 LOAEL = 50 NOAEL = 25 (mouse) NOAEL = 10 (highest dose tested) NOAEL = 10 (highest dose tested)
Genetic Toxicity – Gene Mutation ***In vitro***	Negative; one equivocal
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	Negative
Genetic Toxicity – Chromosomal Aberrations ***In vivo***	Negative in rats; equivocal in mice
Additional Information **Skin Irritation** **Eye Irritation** **Sensitization**	 Not irritating Slightly irritating Not sensitizing in guinea pigs: sensitizing in humans

Appendix B: Screening-Level Exposure Characterization

SPONSORED CHEMICAL

1,3-Diphenylguanidine (CASRN 102-06-7)
(CA Index Name: Guanidine, N,N'-diphenyl)

This exposure characterization was completed using both public, non-confidential sources, and one or more IUR submissions that were available as of this writing.

Volume and Use Information

1,3-Diphenylguanidine had aggregated production and/or import volumes in the U.S. between 1 and 10 million pounds. Non-confidential information in the IUR indicates that this chemical was manufactured and/or imported by the following companies:

- Flexsys America L.P.
- Prochimie International, Inc.
- Rhein Chemie Corporation
- Sovereign Chemical Company
- Sumitomo Corporation of America

There may be other companies that are claimed confidential. Persons submitting IUR information for 2005 asserted that some or all of the information was confidential. Only non-confidential versions of reported IUR data are included in this summary.

Table 1 at the end of this summary lists the non-confidential industrial processing and uses from IUR submissions. Table 2 at the end of this summary lists the non-confidential commercial/consumer uses from IUR submissions.

The HPV submission for this chemical indicated that it is used as an accelerator in vulcanization of rubber and sulfur-containing compounds.[4]

Information from the HSDB indicates that the chemical is used as a vulcanization accelerator for natural and synthetic rubbers, or an activator for other rubber accelerators.[5]

Environmental Releases

Environmental releases may impact general population and environmental exposures. Factors affecting releases include volumes produced, processed and used; numbers of sites; and processes of manufacture, processing, and use.

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4 MLPC, 2003. High Production Volume (HPV) Challenge Submission – SIDS Initial Assessment Profile, Diphenyl guanidine. Accessed 8/8/08. http://www.epa.gov/chemrtk/pubs/summaries/13dphnlg/c14886tp.pdf.
[5] HSDB, 2008. Hazardous Substances Data Bank. Accessed, 8/8/08. Guanidine, N,N'-diphenyl. http://toxnet.nlm.nih.gov/.

Based on IUR data, the maximum total number of industrial sites manufacturing, processing, or using this chemical is confidential.

The following release statements are made based on inferences regarding the non-confidential use information reported in IUR and summarized in Table 1 below.

Many chemicals designated by IUR to have industrial use as "product component" or "incorporation into article" have industrial releases that are a relatively low percentage of the volume. The actual percentage and quantity of release of the reported chemical associated with this category is not known.

Chemicals designated by IUR to have industrial use as process regulators in vulcanization or polymerization processes, or other, can have variable release percentages during industrial processing and use. The actual percentage and quantity of release of the reported chemical associated with this category is not known.

The chemical is not on the Toxics Release Inventory.[6]

Experience has shown that air releases due to volatilization have not been an issue for chemicals with vapor pressures below 0.01 mm Hg. The vapor pressure for 1,3-diphenylguanidine is 1.3 x 10^{-8} mmHg.

Exposures to the General Population and the Environment

Based on the information under the release section above, it is possible there may be potential releases although the quantities and media of releases are uncertain. A search of additional relevant databases did not provide any further information on releases of this chemical.

The IUR ranking for general population and the environment is high due to the likelihood that there will be exposure to this chemical based on the use codes in the IUR data (see Table 1).

1,3-Diphenylguanidine exists primarily as its conjugate acid (the corresponding guanidinium cation) under environmental conditions. The rate of hydrolysis is expected to be negligible under environmental conditions. The rate of atmospheric photodegradation is considered to be moderate. 1,3-Diphenylguanidine is expected to have moderate persistence (P2) and low potential for bioaccumulation (B1).

Based on the information considered, including environmental fate, known uses, and the Agency's expert judgment, EPA identifies, for purposes of risk-based prioritization, a high potential that the general population and the environment might be exposed to 1,3-diphenylguanidine.

[6] USEPA, 2008. Toxic Release Inventory. Accessed, 8/8/08. http://www.epa.gov/triexplorer/.

Exposures to Workers

Worker exposures may be impacted by many factors, including but not limited to volumes produced, processed and used; physical forms and concentrations; processes of manufacture, processing, and use; chemical volatility, and exposure controls, such as engineering controls and personal protective equipment.

Based on IUR data, the maximum total number of workers reasonably likely to be exposed to this chemical during manufacturing and industrial processing and use may be 1,000 or greater. This estimate does not include potentially exposed commercial workers.

The National Occupational Exposure Survey (NOES), conducted from 1981 to 1983, estimated a total of 28,142 workers potentially exposed to this chemical.[7]

Differences between numbers of workers estimated by IUR submitters and by the NOES are attributable to many factors, including time, scope, and method of the estimates. For example, NOES estimates are for all workplaces while IUR are for industrial workplaces only, and NOES used a survey and extrapolation method while IUR submitters simply provide their best estimates based on available information for the specific reporting year.

Based on IUR data, the chemical is manufactured in dry powder, pellets, or in large crystal forms, and worker exposures are possible for this chemical in these forms. There may be other physical forms that are claimed confidential. Also, the non-confidential maximum concentration is greater than 90%. There may be other concentrations that are claimed confidential.

The vapor pressure for 1,3-diphenylguanidine is 1.3×10^{-8} mmHg. Experience has shown that worker exposures due to volatilization have not been an issue for chemicals with vapor pressures below 0.01 mm Hg.

This chemical does not have OSHA Permissible Exposure Limits (PELs).[8]

Based on the information considered, including IUR data and information from the HSDB, and in combination with the Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a high relative ranking for potential worker exposure. This relative ranking is based on the potential for exposure to particulates, and the relatively high number of potentially exposed workers (> 1,000 workers) at manufacturing, and industrial processing and use sites.

Exposures to Consumers

The non-confidential commercial and consumer uses included in the IUR submissions are: rubber and plastic products. Table 2 at the end of this summary provides additional details.

[7] NIOSH, 1983. National Occupational Exposure Survey (NOES, 1981-1983). Accessed, 8/8/08. http://www.cdc.gov/noes/.

[8] NIOSH 1988. OSHA PEL Project Documentation. Accessed, 8/8/08. http://www.cdc.gov/niosh/pel88/npelcas.html.

Other public data sources show uses in rubber vulcanization.

This chemical was listed in the Source Ranking Database (SRD), which indicates that this chemical was contained in one or more consumer products.[9] There is potential that consumers might be exposed to this chemical from consumer products containing this chemical.

EPA identifies, for the purposes of risk-based prioritization, a high potential that consumers might be exposed to this chemical from products containing this chemical, based on the IUR data and on information from public data sources.

Exposures to Children

Persons submitting IUR information reported that children's use information is Not Readily Obtainable.

Based on non-confidential IUR data, the commercial and consumer uses are in rubber and plastic products. There is potential that children might be exposed to this chemical through their use, or through household use, of consumer products containing this chemical.

Other public data sources show uses in rubber vulcanization.

This chemical was listed in the SRD, which indicates that this chemical was contained in one or more consumer products.[10] There is potential that children might be exposed to this chemical from consumer products containing this chemical.

EPA identifies, for the purposes of risk-based prioritization, a high potential that children might be exposed to this chemical from products containing this chemical, based on the IUR data and on information from public data sources.

[9] USEPA 2003. Source Ranking Database (SRD). Accessed, 8/8/08. http://www.epa.gov/opptintr/exposure/pubs/srd.htm.
[10] USEPA 2003. Source Ranking Database (SRD). Accessed, 8/8/08. http://www.epa.gov/opptintr/exposure/pubs/srd.htm.

Non Confidential IUR Data Summary	**1,3-Diphenylguanidine (CASRN 102-06-7)**
Manufacturing/Import Information	
Production (including import) volume:	1 million to 10 million pounds
List of non-CBI companies*:	Flexsys America L.P. Prochimie International, Inc. Rhein Chemie Corporation Sovereign Chemical Company Sumitomo Corporation of America
Maximum number of exposed workers**:	1,000 or greater
Highest non-CBI maximum concentration*:	greater than 90%
Non-CBI physical forms*:	dry powder, pellets or large crystals

* There may be other companies, concentrations and physical forms that are claimed confidential.
** Includes all manufacturing and industrial processing and use workers. There may be additional potentially exposed industrial workers that are not included in this estimate since not all submitters were required to report on industrial processing and use and/or there may be at least one use that contains a "Not Readily Obtainable" (NRO) response among the submissions.

Table 1 Industrial Processing and Use Information		
Processing Activity	**Industrial Sector**	**Function in Industrial Sector**
Processing--incorporation into article	Rubber and Plastics Hoses and Belting Manufacturing	Process regulators, used in vulcanization or polymerization processes
Processing--incorporation into article	Tire Manufacturing	Process regulators, used in vulcanization or polymerization processes
Processing--incorporation into article	Other Rubber Product Manufacturing	Process regulators, used in vulcanization or polymerization processes
Processing--incorporation into formulation, mixture, or reaction product	Tire Manufacturing	Process regulators, used in vulcanization or polymerization processes
Processing--repackaging	Other Rubber Product Manufacturing	Other
One or more items may have been claimed as confidential.		

Table 2 Commercial/Consumer Use Information		
Commercial/Consumer Product Category Description	**Highest Maximum Concentration Range**	**Use in Children's Products**
Rubber and plastic products	Greater than 90%	NRO
One or more items may have been claimed as confidential.		